REMARKS

In view of the above amendments and following remarks, reconsideration of the outstanding office action is respectfully requested.

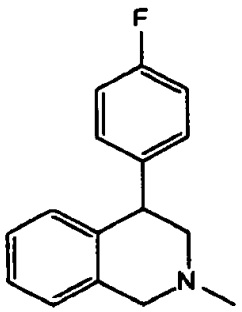
The rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 102(b) as anticipated by Tirelli, et. al., "Differential Effects of Direct and Indirect Dopamine Agonists on the Induction of Gnawing in C57B1/6J Mice", J. Pharm. & Exper. Therap. 273(1): 7-16 (1995)("Tirelli"), Salama, et. al., "Antigenic Determinants Responsible for the Reactions of Drug-Dependent Antibodies with Blood Cells," Brit. J. Haemotol. 78: 535-39 (1991)("Salama"), Swiss Patent Application Serial No. 538477 to F. Hoffmann-LaRoche ("Swiss Application"), or German Patent Application Serial No. 2,062,001 to F. Hoffmann-LaRoche ("German Application") is respectfully traversed for the reasons noted in the amendment filed on November 5, 2002. In addition, since claims 51-92 do not call for R^3 or R^4 to be $-OR^{11}$, these claims are additionally distinguishable from Tirelli, Salama, the Swiss Application, and the German Application on that basis. For all of these reasons, the rejection under 35 U.S.C. § 102(b) for anticipation by these references should be withdrawn.

The rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 103 for obviousness over the German Application or Japanese Patent Application Serial No. 4193867 to Nippon Shinyaku Co. Ltd. ("Japanese Application") is respectfully traversed for all the reasons noted above and in the November 5, 2002, Amendment.

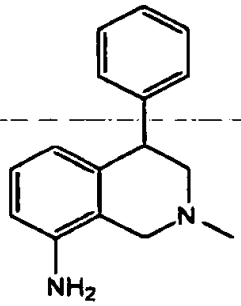
The rejection of claims 30 and 33-34 under 35 U.S.C. § 103 for obviousness over Trepanier, et. al., "3,4-Dihydroisocarostyril and 1,2,3,4-Tetrahydroisoquinoline Derivatives of Ephedrine," J. Med. Chem. 16(4): 342-47 (1973)("Trepanier"), Canadian Patent Application Serial No. 2,015,114 to Mondeshka, et. al., ("CA 2015114"), or Miller, et. al., "An Efficient Synthesis of 4-Aryl-1,2,3,4-Tetrahydorisoquinolines," Syn. Commun. 24(8): 1187-93 (1994) is respectfully traversed for the reasons noted in the November 5, 2002, Amendment.

The accompanying Second Declaration of Bruce F. Molino under 37 C.F.R. § 1.132 ("Second Molino Declaration") is submitted to demonstate that the compounds of the present application achieve greater potency for the norepinephrine transporter ("NET") and dopamine transporter ("DAT") than does compound 1 from CA 2015114 (Second Molino Declaration ¶ 4).

In particular, in addition to the compounds of the present invention (identified below as the PH-7032 compounds), the following compounds were tested:



reference CA 2015114
1



Nomifensine
2

As noted in the Amendment filed by applicants on November 5, 2002 (page 22), since R^3 and R^4 cannot both be H in the claimed invention, CA2015114 does not suggest the claimed invention. As demonstrated below, based on testing set forth in the Second Molino Declaration, the compound of this reference also fails to meet the claimed binding affinity for serotonin transporter protein to a binding affinity for norepinephrine transporter protein ratio of at least 20:1, and, therefore, would not be potent or efficacious for the treatment of depression, ADHD, and other CNS disorders where blocking transporter uptake is implicated. These tests involve the binding assays described in paragraphs 6 and 7 of the Second Molino Declaration. The results of these binding assays for the various compounds tested are set forth in Tables 1 and 2 below.

Table 1

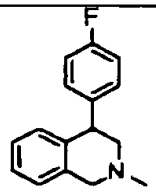
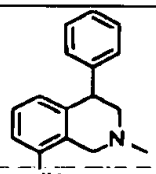
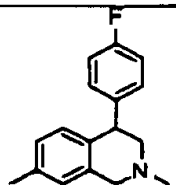
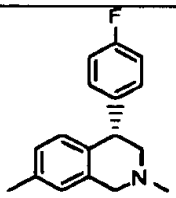
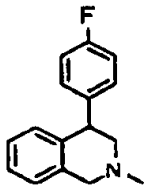
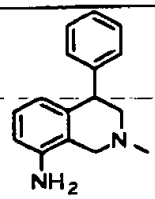
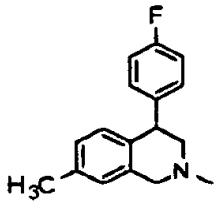
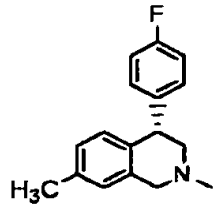
Compounds	NET, Ki nM	DAT, Ki nM	Selectivity DAT/NET
 1 racemate	52	256	4.9
 2 Nomifensine	23	72	2.25
 PH-7032 compound racemate	15	76.5	5.1
 PH-7032 compound (S)-(+)-enantiomer	7.1	36	5.1

Table 2

Compounds	NET, Ki nM	SERT, Ki nM	Selectivity SERT/NET
 **1** reference CA 2015114	52	439	8.4
 **2** Nomifensine	23	1036	45
 PH-7032 compound racemate	15	396	26.4
 PH-7032 compound (S)-(+)-enantiomer	7	231	33

The results in Table 1 demonstrate that compound 1 is approximately: (1) three-fold less potent for NET (based on the NET, Ki value) than the PH-7032 compound racemate and seven-fold less potent than the PH-7032 compound (S)-(+)-enantiomer shown in Table 1 and (2) threefold less potent for DAT (based on the DAT, Ki value) than the PH-7032 compound

racemate and sevenfold less potent than the PH-7032 compound (S)-(+)-enantiomer shown in Table 1 (Second Molino Declaration ¶¶ 8-9).

Compound 2, known as Nomifensine, has demonstrated efficacy in the treatment of depression (Brogden, R.N. et al *Drugs*, 18(1):1-24 (1979)) and attention deficit hyperactivity disorder in clinical trials (ADHD, Shekim, W.O. et al. *J. Nerv. Ment. Dis.*, 177:296 (1989)) (Second Molino Declaration ¶ 10). The efficacy of this clinical agent is attributed to the potency and selectivity of Nomifensine for blocking the NET and the DAT (Id.). Nomifensine was tested separately in the same transporter assay with compound 1 and PH-7032 compounds (Id.). Comparison of the NET and DAT Ki values for Nomifensine with the PH-7032 compounds shows that the values are more closely matched by the PH-7032 racemate than the compound 1 racemate (Id.). Furthermore, the PH-7032 compound (S)-(+)-enantiomer possesses even better potency for NET and DAT than Nomifensine, the PH-7032 compound racemate, and compound 1 (Id.). As a result of this unexpected increase in potency for blocking the NET and DAT, one would expect that the PH-7032 compounds, especially the (S)-(+)-enantiomer would be as potent or more efficacious than Nomifensine for the treatment of depression, ADHD, and other CNS disorders where blocking transporter uptake is implicated (Id.). On the other hand, compound 1 would not be expected to be as potent nor as efficacious as Nomifensine or PH-7032 (Id.).

The results in Table 2 demonstrate that compound 1 does not achieve a binding affinity for serotonin transporter protein to a binding affinity for norepinephrine transporter protein ratio of at least 20:1 (Second Molino Declaration ¶ 11). Moreover, this compound is less selective for the NET vs. the SERT than compound 2, the PH-7032 compound racemate, or the PH-7032 compound (S)-(+)-enantiomer, based on ratios of the Ki values (SERT, Ki / NET, Ki) (Id.). The class of drugs known as serotonin selective reuptake inhibitors ("SSRI"), exemplified by the antidepressant Prozac™, are associated with side effects like sexual dysfunction in many patients (Id.). The compounds of the present invention, like PH-7032 compound racemate or PH-7032 compound (S)-(+)-enantiomer, possess greater potency and selectivity for blocking the NET and DAT vs. the SERT and would be expected to possess fewer side effects due to the lack of effect on serotonin (Id.).

Accordingly, for all of the reasons set forth in the Amendment filed on November 5, 2002, as well as those noted above, the rejection based on CA 2015114 should be withdrawn.

The rejection of claims 30 and 33-34 under 35 U.S.C. § 103 for obviousness over Tirelli is respectfully traversed for the reasons noted in the November 5, 2002, amendment.

The rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed for the reasons noted in the November 5, 2002, amendment.

The rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 112 (1st para.) is respectfully traversed for the reasons noted in the November 5, 2002, amendment.

In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: June 12, 2003

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